MRS in Neurodegenerative Disease

Adam D Waldman MD PhD

Charing Cross Hospital and Dementia Research Group, Institute of Neurology. London UK

Introduction

MRS is most likely to provide most added diagnostic value in the investigation of diseases where structural imaging is of limited sensitivity and/or specificity; it is therefore well suited to the study of neurodegenerative diseases, in particular primary dementias.

These are groups of conditions where any structural changes which are evident on anatomical imaging sequences generally correlate poorly with clinical diagnostic categories, underlying pathophysiology and disease severity. T_1- and T_2-dependent MR sequences which are the mainstay of routine clinical neuroimaging are frequently insensitive to the underlying pathological processes in these diseases. Focal or global atrophy due to associated neuronal loss is also frequently subtle or absent, particularly early in the course of disease.

As a result, clinical brain imaging using standard techniques is frequently either normal, or non-specifically abnormal.

MRS can be considered to have two main purposes:

Clinical: To provide diagnostic information which augments that available from clinical examination, laboratory tests and conventional structural brain imaging. The aim is to increase the sensitivity and or specificity of the imaging examination as a whole, and improve diagnostic confidence, which will ultimately guide clinical management. In this context, the technique must provide a surrogate marker of disease. In practice, this requires sufficient separation between metabolite measures to allow an individual patient to be placed confidently in a particular diagnostic or prognostic clinical group. In order to have widespread clinical impact, the technique must improve specificity, sensitivity, safety or cost-efficacy in securing a diagnosis. A related application is in the provision of surrogate markers of disease progression and therapeutic response. As this involves longitudinal measures, the stability of the technique and normal physiological variation in comparison to the magnitude of biological changes being examined are key issues. It is also worth commenting that statistically significant differences between clinical groups, even if there is overlap between them, may be valuable in evaluation of therapy, as therapeutic response is frequently only reflected in group-analyses.

Scientific: Toward better understanding of pathological changes in the brain, their anatomical distribution and how they manifest as clinical disease. Although the statistical demands in terms of separation of groups may be less, more rigorous interpretation of the measured physiological parameters in terms of the underlying disease process is required.

Particular challenges to MRS in neurodegenerative disease

Diagnostic Validation

Validation of diagnosis is difficult in the study of patients with neurodegerative diseases, where definitive diagnosis relies on characteristic histopathology in brain

parenchyma. Because of limited treatment options, the morbidity and mortality associated with brain biopsy is rarely justified in this clinical population. Any pathological examination is therefore usually *post mortem*, which for chronic diseases may be several years later; hence, interpretation may be confounded by the normal aging process and other intercurrent pathology.
The situation is easier in those relatively rare conditions where a specific gene has been identified as a cause, although phenotypic expression of the underlying genetic abnormality may be highly variable.
Many neurodegenerative conditions are diseases of the elderly. It is important to distinguish changes in metabolites due to the pathology of interest from those related to normal aging, co-morbidity and intercurrent medication, which are also very much more common in older people.

Technical and Practical Issues
Particularly relevant to the study of neurodegenerative disease.
Total examination time should be kept to a minimum (ideally less than 45 minutes), and maximum effort made to ensure subjects who are often elderly are as comfortable as possible in the magnet. Degenerative kyphosis of the neck can present particular problems with positioning within a headcoil.
By the nature of neurodegenerative and psychiatric diseases, patients may be confused or agitated and may experience involuntary movements; safety in the scanner and problems with subject motion may therefore be significant issues.
These factors affect the technical quality of the study, patient experience and compliance.

MRS in Alzheimer's Disease
Reduced levels of N-acetyl aspartate (NAA) and elevated *myo*-inositol (mI) in the posterior cingulate region of subjects with probable AD were first reported from short echo time (TE) single voxel studies in the early 1990s. Since then a large number of studies of MRS in AD have been published using both single voxel and CSI methods, the latter predominantly at long TE. These have allowed regional metabolite abnormalities in AD to be investigated.
The most consistent finding is of reduced NAA and elevated mI, reflected in both metabolite ratios to Cr and absolute concentrations.

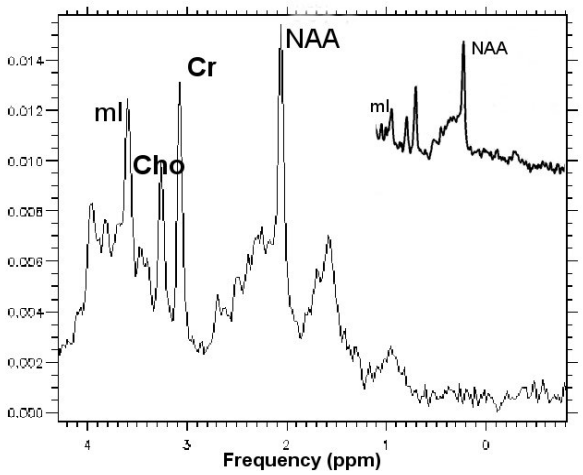
Decreased NAA

The regions of the brain in which pathological changes of AD are prominent, such as the mesial temporal lobe, entorhinal cortex, hippocampus and the limbic system demonstrate decreases in NAA earlier in the disease. This is reflected in patterns of regional atrophy demonstrated on serial volumetric MRI studies. Abnormalities in the visual cortex and primary motor and sensory areas are only present with very advanced disease. The mean reported decrease in NAA is around 10%, compared to normal subjects. MRSI studies provide information regarding regional distribution of changes in metabolite concentrations and thereby avoid the potential problems with sampling errors that may occur with single voxel techniques. NAA, Cho and Cr are the metabolites most commonly mapped by MRSI. Schuff et al [4] demonstrated decreased levels of NAA in the mesial temporal lobes, including the hippocampus and parietal grey matter but not in the frontal lobes or white matter, which agreed with the known distribution of the pathological changes in AD.

NAA is thought to be synthesised solely within the mitochondria of neurons, and is therefore only seen within these cells and their axons. Despite being one of the more abundant amino acids in the central nervous system, NAA was not discovered until 1956; the development of *in vivo* MRS has stimulated further interest in the biochemistry of this metabolite, but its true function in the brain remains incompletely understood. Pathologically reduced brain NAA is widely accepted as a marker of neuronal loss or dysfunction. *Ex vivo* spectroscopy measurements have shown [NAA] to correlate with neuronal density in brain tissue from patients with AD. However, transient loss of NAA following acute cerebral insult, for example in epilepsy, after head injury and acute demyelinating disease, also suggests that perturbation of mitochondrial function, on which NAA synthesis depends, may cause a reversible fall in the metabolite in viable neurons.
NAA is therefore better thought of as a marker of healthy neuronal integrity and that reduction in NAA levels is in itself, a non-specific finding in regions of brain which have suffered a wide range of insults.
Some normalisation of NAA levels in patients with AD who have been treated with acetyl cholinesterase inhibitors suggest that neuronal dysfunction of viable neurons may in part be responsible for the decrease in NAA which is a feature of this disease.

Elevated mI

Because of it's relatively short T_2, *myo*-inositol (mI) can only be detected and measured reliably at short TE (< 40ms, and ideally 30ms or less).Until recently, commercial CSI/MRSI sequences have only supported acquisition at TE > 100ms and so evaluation of this metabolite in dementia has therefore largely been limited to single voxel (SV) studies.
Elevation of mI has been shown in patients with AD at an earlier stage than the decrease in NAA and affects the mesial temporal lobe first. Short TE studies in this region of the brain are particularly technically challenging, and mI determination is prone to errors. More reliable mI measurements have been made in the anterior and posterior cingulate gyrus and cerebral white matter. The mean magnitude of increase is in the order of 20%.
Myo-inositol is a pentose sugar that is involved in the inositol triphosphate intra-cellular second messenger cycle. The pathophysiological significance of mI elevation in the context of primary degenerative dementias remains unresolved. A leading hypothesis is that it reflects increased populations of glial cells which express higher levels of this metabolite than neurons; this may be related to differences in *myo*-inositol/Na co-transporter activity which appears to play a key role in osmoregulation in astrocytes.
Although elevation of mI in the context of cerebral insult is again not highly specific to the pathology of AD and may be seen in other conditions, an increase within specific regions of cortical grey matter does appear to be a characteristic feature of primary neurodegenerative disease.



Short TE single voxel spectrum from a subject with clinical AD, showing decresed NAA and increased MI compared to normal spectrum (inset).

Other metabolites: Glx, Cho and Cr

Glx (corresponding to a composite of signals from glutamine, Gln, and glutamate, Glu) resonances are heavily J-coupled, and hence are also only detected well at short TE. Conflicting reports have been published concerning the behaviour of Glx levels in AD. Significantly decreased Glx levels in the occipital cortex of patients with AD have been interpreted as reflecting neuronal loss. However, on other study demonstrated a statistically significant increase in Glx/Cr in the temporal lobe (encompassing both grey and white matter) and similar increase in the parietal grey matter which did not reach statistical significance.

Glx is difficult to measure reliably at 1.5T, at which most studies have been performed, due to its complex multiplet resonances; these are coalesced at lower field strengths and more easily resolved as a single broad peak, although reliability of metabolite quantification in this situation has not been widely validated. A more recent study at 3T, where the increased frequency resolution allows more reliable evaluation of these metabolites supports the view that Glx/Cr is lower, and correlates with decreased NAA/Cr in AD; this effect was more pronounced in grey matter than in white matter. To date, the interesting question as to whether the inhibitory neurotransmitter Gln, excitatory neurotransmitter, Glu or both change pathologically awaits technical advances which will allow independent measurement of their concentrations.

Inconsistent findings have been reported with regard to Cho levels in AD; some studies have shown higher levels in AD compared to controls, whilst others found no difference. This is perhaps surprising in view of the known dysfunction in cholinergic neurotransmission in AD, which is the rationale for the use of cholinesterase inhibitor therapy in this disease. It must be assumed that other choline-containing moieties dominate the Cho signal.

Cr is frequently used as an internal reference to which ratios of other metabolites are expressed. No significant differences in [Cr] have been shown in age-matched populations of AD and control subjects. There is, however, evidence that [Cr] varies independently with age and cognitive impairment. Cr changes are therefore a possible confounding variable, and measurement of metabolite concentrations independent of [Cr] will help to clarify which combination of metabolites are most sensitive and specific in AD.

NAA and mI in the diagnosis of AD

The combination of decreased NAA with increased mI is in keeping with a diagnosis of AD. The derived metabolite ratio NAA/mI has been shown to be a useful diagnostic index for AD. The diagnostic power has varied between published series; sensitivities and specificities of 83% and 98%, and 82% and 80% have been reported. NAA/mI also provides a metabolic index which is independent of [Cr] without the necessity of calculating absolute metabolite concentrations.
The incorporation of Glx may potentially improve the power of MRS to discriminate between normal and AD subjects, but as discussed above, determination of Glx is not at present sufficiently reliable to make this useful clinically on 1.5T scanners. More widespread availability of 3T MRI equipment may overcome this problem.

Choice of voxel location

Although pathological changes may predominate in the mesial temporal structures early in disease, technical considerations favour the posterior cingulate region as the target for single voxel MRS examination, where high quality, reproducible short TE spectra can be acquired. It is also a region in which pathological changes occur throughout the course of disease.

Acquisition parameters

Short TE is essential for detection of mI, the discriminant resonance in most primary degenerative dementias.
There is no clear consensus as to the optimum TR. Relatively short TR (1500-2000ms) helps to minimise acquisition times in this potentially non-compliant group of patients, but introduces a degree of T1-weighting to the spectra.
The use of local metabolite standards and ongoing MRS quality assurance is necessary as differences in metabolite ratios may occur between scanners, and with time.

Quantification methods

Absolute metabolite quantification allows individual metabolite levels to be determined independently and is hence useful scientifically, but involves correcting for CSF within the voxel, introduces errors and is generally less reproducible than metabolite ratio determinations.
Automated, on-line semiquantitative measurements which are available as part of most commercial MRS packages usually yield ratio data which are reproducible and robust for clinical use.

MRS for Distinguishing Common Dementias

AD – Alzheimer's Disease
FTLD – Fronto-Temporal Lobar Degeneration
DLB – Dementia with Lewy Bodies
VaD – Vascular dementia
MCI – Mild cognitive impairment

MRS studies from the posterior cingulate region shown that, compared to age-matched normal subjects, patients with AD, FTLD and VaD show decreased NAA/Cr.

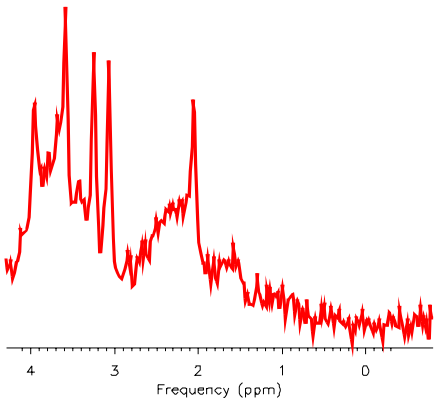
MI/Cr, however, is only raised in AD and FTLD. Cho/Cr is elevated in patients with AD, and FTLD and, more convincingly, in DLB.
These data have been interpreted in terms of the known pathological changes in the different diseases; decreased NAA in conditions associated with neuronal loss (AD, FTLD, VaD), increased MI in those with gliosis (AD, FTLD) and increased Cho in those with marked cholinergic deficit (e.g. AD and DLB).
Subjects with MCI (who are at high risk of developing AD) show elevated MI/Cr, but normal NAA, suggesting that MI may be a early marker of AD pathology; longitudinal studies support this model.

	AD	**FTLD**	**VaD**	**DLB**	**MCI**
NAA	⇓⇓	⇓⇓	⇓⇓	-	-
MI	⇑⇑	⇑⇑	-	-	⇑
Cho	(⇑)	(⇑)	-	⇑	-

Summary or posterior cingulate MRS metabolite abnormalities (after Kantarci et al 2004)

Prion Disease

A number of studies of MRS in prion disease have been published, mostly isolated case reports in sporadic Creutzfeldt Jakob Disease (CJD) and familial disease using long TE techniques. The most consistent finding was of quite marked, but non-specific reduction in NAA in various regions of the brain. Short TE measurements from the thalami of variant CJD patients have shown striking elevation of mI (mean 2.5 fold increase) and very low NAA. They have been attributed to the severe neuronal depletion and intense gliosis, which are pathological features of this brain region in vCJD.



Short TE spectrum from thalamus of a patient with variant CJD, showing extremely high MI and low NAA.

MRS in Neurodegeneration (Movement disorders etc)

Parkinsonian syndromes

No role has emerged for MRS in the clinical investigation of degenerative movement disorders. To date, the findings in the most common of these, Idiopathic Parkinson's Disease (IPD), are inconsistent and those in other parkinsonian syndromes, notably multisystem atrophy (MSA) and progressive supranuclear palsy (PSP), differences are not sufficiently specific or discriminant to be useful diagnostically.

Motor Neuron Disease/Amyotrophic Lateral Sclerosis

Decreasing NAA, Cho and Cre levels have been demonstrated in the motor cortex most affected clinically in patients with MND, although the magnitude of change limits diagnostic use in an individual patient.

Summary Points

- **Short TE single voxel MRS is a useful diagnostic test for AD**
- **Posterior cingulate region provides robust acquisition and data**
- **MI/NAA is the discriminant metabolite ratio**
- **Discrimination from vascular dementia fair, but from other primary dementia may be difficult**
- **No current clinical role for MRS in other neurodegenerative disease**

Key References:

Alzheimer disease: depiction of increased cerebral myoinositol with proton MR spectroscopy. Miller, BL *et al* Radiology 1993; **187**: 443-447.

Selective reduction of N-acetylaspartate in medial temporal and parietal lobes in AD. Schuff N *et al* Neurology. 2002; 58 928-35

^{1}H MR spectroscopy in common dementias
Kantarci K *et al* Neurology 2004; 63 1393-1398

Reviews and Bibliography:

^{1}H MRS evaluation of metabolism in alzheimer's disease and vascular dementia
Jones RS Waldman AD. Neurol Res. (2004) 26:488-95

Kantarci K and Jack CR (Chapter 34; MR spectroscopy in aging and dementia) and Davie C (Chapter 35; **Magnetic resonance spectroscopy in neurodegeneration**) in Clinical Neuroimaging, Diffusion, Perfusion, Spectroscopy; Gillard JH, Waldman AD, Barker PB eds. Cambridge University Press (2004).